Remarks

Claims 26-33 and 59-66 are pending. Claims 34 and 67 have been cancelled. Claims 26, 29, 30, 33, 59, 62, 63, 65, and 66 have been amended to clarify the claimed subject matter and provide proper antecedent basis. Support for the amendment to claims 29 and 62 can be found, for example, at page 3, paragraph 0012, wherein the physical and functional properties of cell surfaces are altered to "inhibit maturation and release of membrane-enveloped viruses" and in further view of the discussion below. Claim 65 has been amended to properly refer to each of SEQ ID NO:1 and SEQ ID NO:2. It should be noted that SEQ ID NO:1 encodes the amino acid sequence of SEQ ID NO:2.

The present invention is directed to methods of inhibiting or preventing viral infection by introducing into viral-infected cell ***or uninfected cells***, respectively, a phospholipid scramblase polypeptide or fragments thereof containing the phospholipid scramblase amino acid motif PPxY. The N-terminal regions of human and mouse phospholipid scramblase 1 share with diverse types of membrane bound viruses late function PPxY motifs required for release of virus particle from cells. The PPxY motifs in phospholipid scramblase 1 suppress virus budding by competing with viral M or Gag proteins for binding to cellular WW domain proteins.

As described in the specification at page 34, paragraph 0110, "inhibiting" refers to, *inter alia*, ***arresting*** the development of disease and/or causing the reduction, remission, or regression of a disease; and "preventing" refers to, *inter alia*, ***stopping the initiation*** of a disease or condition. Of course, prevention relates to **preemptively** stopping viral **infection**, and therefore uninfected cells are treated as a preemptive measure against infection. Furthermore, arresting the

development of disease, relies upon a sufficient **reactive** measure (a certain number of cells have already been infected). The disease needs to be reduced, or put into regression.

Rejection Under 35 U.S.C. § 112, first paragraph

Claims 26-34 and 59-67 were rejected under 35 U.S.C. § 112, first paragraph, as not being enabled. Applicants respectfully traverse this rejection to the extent that it is applied to the claims as amended.

The Legal Standard for Enablement

The Court of Appeals for the Federal Circuit (CAFC) has described the legal standard for enablement under § 112, first paragraph, as whether one skilled in the art could make and use the claimed invention from the disclosures in the patent coupled with information known in the art, without undue experimentation (*See, e.g., Genentech, Inc. v. Novo Nordisk A/S*, 108 F3d at 165, 42 USPQ2d at 1004 (quoting *In re Wright*, 999 F.2d 1557, 1561, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993); See also *In re Fisher*, 427 F.2d at 839, 166 USPQ at 24; *United States v. Telectronics, Inc.*, 857 F.2d 778 (Fed. Cir. 1988); *In re Stephens*, 529 F.2d 1343 (CCPA 1976)). The fact that experimentation may be complex does not necessarily make it undue, if the art typically engages in such experimentation (*M.I.T. v. A.B. Fortia*, 774 F.2d 1104 (Fed. Cir. 1985)). In addition, as affirmed by the Court in *Spectra-Physics, Inc. v. Coherent, Inc.*, 827 F.2d 1524 (Fed. Cir. 1987), a patent need not teach, and preferably omits, what is well known in the art.

Whether the disclosure is enabling is a legal conclusion based upon several underlying factual inquiries. See *In re Wands*, 858 F.2d 731, 735, 736-737, 8 USPQ2d 1400, 1402, 1404

(Fed. Cir. 1988). As set forth in *Wands*, the factors to be considered in determining whether a claimed invention is enabled throughout its scope without undue experimentation include the quantity of experimentation necessary, the amount of direction or guidance presented, the presence or absence of working examples, the nature of the invention, the state of the prior art, the relative skill of those in the art, the predictability or unpredictability of the art, and the breadth of the claims. In cases that involve unpredictable factors, "the scope of the enablement obviously varies inversely with the degree of unpredictability of the factors involved." *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970). The fact that some experimentation is necessary does not preclude enablement; what is required is that the amount of experimentation 'must not be unduly extensive.' *Atlas Powder Co., v. E.I. DuPont De Nemours & Co.*, 750 F.2d 1569, 1576, 224 USPQ 409, 413 (Fed. Cir. 1984). There is no requirement for examples.

The claims are directed to inhibiting/preventing virus budding *via* a Phospholipid Scramblase polypeptide or fragment thereof. The examiner asserts that the results of Example 4 are ambiguous for whether the cytokine or the enzyme had a direct effect on VSV replication. The applicants readily admit that IFN is known to inhibit VSV at different stages in its life cycle by different anti-viral pathways. The results in Example 4 indicate that the phospholipid scramblase ***cooperates*** with other IFN-induced proteins in the inhibition of VSV replication (see paragraph 0139). However, as shown in the preceding paragraph (0138) and previously stated by the applicants, the viability of phospholipid scramblase cDNA expressing cells was 33% (compared to that of vector control cells: 7%). The assay was conducted using VSV stably

transfected HEY 1B cells. "Therefore, expression of PLSCR1 resulted in a significant reduction in the cytopathic effect of VSV infection" (see last sentence of paragraph 0138; wherein no cytokine was present). At an MOI of 10 pfu (10 plaque forming units roughly equal to 10 viruses per cell), a 26% increase in viable cells ***is statistically significant*** (33% - 7% = 26%). The results of Example 4 clearly show an inhibition, or regression, of the disease state of the transfected cell line. Again, "inhibiting" refers to, *inter alia*, ***arresting*** the development of disease and/or causing the reduction, remission, or regression of a disease. The applicants readily admit that the results of example 4 do not relate to preventing disease ("preventing" refers to, *inter alia*, ***stopping the initiation*** of a disease or condition), because the host cells were ***already*** transfected. In view of the foregoing, the applicants respectfully submit that a method of inhibiting viral infection comprising, introducing into cells a Phospholipid Scramblase polypeptide or fragment thereof, wherein the polypeptide or fragment thereof contains the amino acid sequence PPxY and prevents virus budding, ***has been reduced to practice*** (delivery and efficacy). Example 4 clearly shows that there was no adverse effect on routine cellular function (addressing examiners concern of page 7, first paragraph, of the office action mailed on February 25, 2003).

There appears to be confusion as to whether the rejection is for enablement or for alleged lack of written description. The examiner asserts that the skilled artisan would be able to make the scope of the claimed genus because the species are structurally unrecognizable (second paragraph, page 7, of the office action mailed on February 25, 2003; applicants assume that the examiner intended to assert that the skilled artisan would NOT be able to make the scope of the

genus). While most of the following does pertain to the written description, any one of ordinary skill in the art would also be enabled, by following the methods described in the specification, using known reagents, without undue experimentation. The specification is replete with examples of peptides harboring the PPxY sequence (in viral species and scramblase species). The presence of the motif enables inhibition of viral budding. Given the technology at the time of filing the present application, one of ordinary skill in the art would be able to synthesize and/or isolate polypeptides having such activity. Furthermore, the targeted protein domain is well characterized (WW domain). Therefore, the structural features common to the claimed PPxY containing scramblases, also defined by the WW domain and the complementary forces it contains for proper binding by the PPxY domain (for example, the requisite hydrogen bonding acceptor and donor sites, electrostatic interactions, and geometric and steric constraints of the WW domain), are known and readily discernable and available to those skilled in the art. In view of the foregoing, **the applicants respectfully assert that the scope of the claimed genus is structurally recognizable, and any artisan skilled in the art in 2001 would have been able to make the claimed scramblases.** As the Federal Circuit said in Amgen v. Hoechst, *supra*, earlier this year, it is a different standard when one is claiming the use of known materials.

Claims 26-34 and 59-67 were rejected under 35 U.S.C. § 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the art that the inventor had possession of the claimed invention. Applicants respectfully traverse this rejection.

The Legal Standard

As the Court of Appeals for the Federal Circuit recently stated in Amgen v. Hoechst, et al. 314 F.3d 1313, 65 USPQ2d 1385 (Fed. Cir. 2003),

"the purpose of the written description requirement is to prevent an applicant from later asserting that he invented that which he did not; the applicant for a patent is therefore required to "recount his invention in such detail that his future claims can be determined to be encompassed within his original creation." Vas-Cath Inc. v. Mahurkar, 935 F.2d 1555, 1561, 19 USPQ2d 111, 1115 (Fed. Cir. 1991). Satisfaction of this requirement is measured by the understanding of the ordinarily skilled artisan. Lockwood v. Am. Airlines, Inc., 107 F.3d 1565, 1572, 41 USPQ2d 1961, 1966 (Fed. Cir. 1997) ("The description must clearly allow persons of ordinary skill in the art to recognize that [the inventor] invented what is claimed."). "Compliance with the written description requirement is essentially a fact-based inquiry that will 'necessarily vary depending on the nature of the invention claimed.'" Enzo Biochem v. Gen-Probe, Inc., 296 F.3d 1316, 1324, 63 USPQ2d 1609, 1613 (Fed. Cir. 2002) (citation omitted)."

The Court of Appeal for the Federal Circuit's decision in Eli Lilly v. Univ. of Calif. Board of Regents In Regents of University of California v. Eli Lilly & Co., 119 F.3d 1559, 43 U.S.P.Q.2d 1398 (Fed. Cir. 1997), *cert denied*, 523 U.S. 1089 (1998) is not applicable in this case. The claims in this case are not drawn to claims to a protein or a gene encoding a protein, but to a method of use of known materials. In Enzo Biochem, the Federal Circuit held that that the written description requirement can be met by a functional description of *claimed materials*, if coupled with a known or disclosed correlation between function and structure. Enzo Biochem,

Inc., v. Gen-Probe, Inc., 296 F.3d 1316, 63 U.S.P.Q.2d 1609 (Fed. Cir.2002) (*"Enzo II"*). Enzo is also not applicable in this case, again since appellant is claiming a method of using known materials, not the materials themselves.

In Amgen, the Federal Circuit upheld the lower court's claim construction and its decision that the claims comply with the written description and enablement requirements of 35 U.S.C. § 112, stating

"Both Eli Lilly and Enzo Biochem are inapposite to this case because the claim terms at issue here are not new or unknown biological materials that ordinarily skilled artisans would easily miscomprehend." Reiterating, the Court stated that the standard was merely that "the patent specification must contain "a written description of the invention, and of the manner and process of making and using it...[such] as to enable any person of ordinary skill in the art to which it pertains ... to make and use the same ... " "The specification does not need to teach what is already known in the art. The specification is enabled if one of ordinary skill in the art only engages in routine experimentation to make the invention."

The examiner has asserted the specification does not disclose representative fragments of the genus claimed comprising the instant PPxY motif that would bind to every WW motif with target proteins to prevent viral infection. As noted previously, the applicant's have cited numerous examples of Phospholipid Scramblases which contain this motif and have provided strong scientific support that one ordinarily skilled in the art would expect fragments harboring the PPxY motif to function similarly. The Examiner is respectfully reminded of the foregoing discussion as it relates to the legal standard for written description. A Phospholipid Scramblase

polypeptide or fragment thereof, containing the amino acid sequence PPxY, is a *known material* in the methods as claimed. Such a sequence motif was in the applicant's possession. Phospholipid scramblases, and in particular the PPxY motifs, have been very well characterized. PPxY motifs in phospholipid scramblase 1 ***suppress and/or inhibit virus budding*** by competing with the viral M or Gag proteins for binding to cellular WW domain proteins. If virus budding is suppressed, it simply *does not matter* if every WW motif in a target protein is actively bound by a PPxY harboring protein (as the Examiner states that it does; see page 5 of the office action mailed on February 25, 2003). The object of each of the claimed methods *is to inhibit or suppress virus budding.*

Not all viruses obtain lipid-containing membranes during maturation (process known as "budding" through the host cell's surface producing an "enveloped" virus). Using the cell's own machinery, these viruses direct the insertion of their surface glycoproteins into the cell membrane. One of ordinary skill in the art will recognize that budding involves a transmembrane interaction of these membrane glycoproteins and the components of the virus in the cytoplasm, followed by pinching off from the cell surface. The lipids in the resulting bilayer derive from the cell, whereas the proteins are virally encoded. It is extremely important to note that the mechanism of release of progeny virus from an infected cell depends on the structure of the virus. It has been generally assumed that unenveloped viruses are released by lysis of the cells (bursting of the cells resulting in discontinuous and fragmented cell membrane; this point is made only to further distinguish enveloped/budding viruses from those viruses that exit cells, or cellular debris, wherein the viruses do not obtain a cell membrane "coat").

In view of the foregoing discussion, there is a clear structural distinction between those viruses that exit infected cells having a cellular membrane "coat" and those that do not. Such a distinction is directly related to virus type (structure), mode of transmission, infectivity and pathology. Any person of ordinary skill in the art will agree with such an assertion.

One of ordinary skill in the art will readily recognize that viruses budding from infected cells can be easily assayed (even microscopically!). The examiner maintains that the skilled artisan would be unable to make the instant polypeptides because the specification does not teach how one could identify any possible fragment of Phospholipid scramblase with the required sequence motif that retains the required activity (see page 5 of the office action mailed on February 25, 2003). The motif has been presented: PPxY. The varying types of scramblases have been presented. Assays and methods of cloning and analyzing sequences were well within the realm of common knowledge at the time of filing the present application (also see, Example 5, wherein BLAST analysis readily identified similar EST clones encoding potential scramblases, wherein chromosomal localization was assessed, wherein tissue distribution was analyzed, and wherein antibody probes are utilized and discussed; also see Examples 6-10).

Again, the applicant is not required, nor is he encouraged, to describe each and every structure which may contain this motif, but rather provide a number of species within a genus to support each claim.

The applicant's respectfully submit that in view of the foregoing discussion, they have met the legal standard for written description.

U.S.S.N. 09/823,847
Filed: March 30, 2001
AMENDMENT AND RESPONSE TO OFFICE ACTION

Rejection Under 35 U.S.C. § 112, second paragraph

Claims 29, 30, 34, 62, 63 and 67 were rejected under 35 U.S.C. § 112, second paragraph, as being indefinite. Applicants respectfully traverse this rejection to the extent that it is applied to the claims as amended.

Claims 30 and 63 were amended to provide proper antecedent basis for the limitations of each claim. Each of claims 29 and 62 were amended to clarify that it is the virally infected cells that release membrane enveloped viruses, wherein the membrane is derived from the virally infected cell. One of ordinary skill in the art will readily recognize that, in many cases of virus egress (or cellular escape after replication), the budding virus is "coated" in the membrane of the cell (please see foregoing detailed discussion as it relates to the known mechanism of virus budding).

Claim Objections

Claims 59-67 were objected to under as being as being of improper dependent form for failing to further limit the subject matter of claims 26-34.

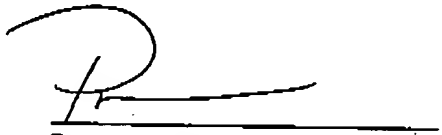
It should be noted that claims 59-67 do not depend from 26-34, and are therefore not required to further limit the subject matter of those claims. The examiner has asserted that "inhibiting" and "preventing" viral infection are not distinguishable. However, as noted at page 34, paragraph 0110, "inhibiting" refers to, *inter alia, **arresting*** the development of disease and/or causing the reduction, remission, or regression of a disease; and "preventing" refers to, *inter alia, **stopping the initiation*** of a disease or condition. Furthermore, "[T]hose of skill in the art will understand that various methodologies and assays may be used to assess the development of a

disease, disorder or condition, and similarly, various methodologies and assays may be used to assess the reduction, remission or regression of a disease, disorder or condition" (see paragraph 0110).

For the foregoing reasons, the applicants respectfully submit that the previously submitted claims 59-67 do NOT encompass the same subject matter of claims 26-34.

Allowance of claims 26-34 and 59-67 is respectfully solicited.

Respectfully submitted,

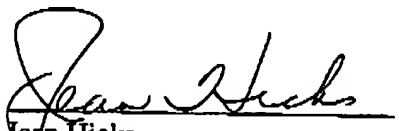


Patrea L. Pabst
Reg. No. 31,284

Date: July 25, 2003
HOLLAND & KNIGHT LLP
One Atlantic Center, Suite 2000
1201 West Peachtree Street
Atlanta, Georgia 30309-3400
(404) 817-8473
(404) 817-8588 (Fax)

Certificate of Facsimile Transmission

I hereby certify that this Amendment and Response to Office Action, and any documents referred to as attached therein are being facsimile transmitted on this date, July 25, 2003, to the Commissioner for Patents, U.S. Patent and Trademark Office, P.O. Box 1450, Alexandria, VA 22313-1450.



Jean Hicks

Date: July 25, 2003